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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Virginia M. Litwin, et al.
U.S. Serial No.:	09/891,062	Examiner: J. Parkin
Filed	: June 25, 2001	Art Unit: 1648
For	: COMPOUNDS CAPABLE OF INHIBITING HIV-1 INFECTION	

1185 Avenue of the Americas
New York, New York 10036

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SIR:

DECLARATION UNDER 37 C.F.R. §1.132 OF RONALD C. KENNEDY

I, Ronald C. Kennedy, Ph.D., hereby declare that:

1. I am a Professor and Chairman of the Department of Microbiology and Immunology at Texas Tech University Health Sciences Center located in Lubbock, Texas. I received a Ph.D. in Microbiology from the University of Hawaii and have 23 years of experience working in the monoclonal antibody field. A copy of my curriculum vitae is attached hereto as **Exhibit 1**.

2. I am an independent consultant to Progenics Pharmaceuticals, Inc. ("Progenics") in Tarrytown, New York, in the field of monoclonal antibodies. I am paid for work which I perform in my capacity as an independent consultant to Progenics.

3. My expertise and experience in making, characterizing and using monoclonal antibodies includes 49 peer review scientific publications since 1982. See my attached curriculum vitae. My research includes generating, using and characterizing monoclonal antibodies against various antigens and epitopes associated with immunoglobulin molecules, infectious agents, and cell surface antigens such as the following: hepatitis B virus surface antigen; herpes simplex virus; HIV-1 envelope glycoprotein; lymphoid cell surface markers; and immunoglobulins from different species. My research also includes generating and using monoclonal antibodies in cancer detection and treatment. See the references listed in **(Exhibit 2)**. My work in characterizing monoclonal antibodies has included the use of monoclonal antibody formulations wherein the monoclonal antibody is a chimeric monoclonal antibody and wherein it is a human monoclonal antibody. I have worked with monoclonal antibodies wherein we have isolated a single chain antibody or an antigen-binding fragment as the relevant reactive site on the monoclonal antibody. My laboratory has also used monoclonal antibodies that are labeled with a detectable marker including a radioactive isotype (I^{131}), an enzyme (horseradish peroxidase), dye (fluorescein isothiocyanate) or biotin. Thus, I am very familiar with the field of making monoclonal antibodies and am knowledgeable about the level of skill of those active in the field.

4. I have also read and am familiar with the specification of the above-identified application.

5. I understand the claimed invention to be a method of inhibiting HIV-1 infection of a CD4+ cell, which method comprises contacting the CD4+ cell with an amount of a monoclonal antibody or portion thereof effective to (a) specifically inhibit 67% or greater of fusion of a CD4+ PM-1 cell to a HeLa cell expressing envelope glycoprotein from HIV-1_{JR-FL} and (b) inhibit 18% or less of fusion of a CD4+ SUP-T1 cell to a HeLa cell expressing envelope protein from HIV-1_{LAI}, wherein the antibody (i) does not cross-react with HIV-1 envelope glycoprotein or CD4, (ii) reacts with an antigen on the surface of a PM-1 cell, and (iii) does not react with an antigen on the surface of a SUP-T1 cell, so as to thereby inhibit HIV-1 infection of the CD4+ cell. Accordingly, the claimed invention relates to a method of inhibiting HIV-1 infection of a CD4+ cell involving contacting the CD4+ cell with a monoclonal antibody having well-defined, specific characteristics whose function is to inhibit fusion in the manner defined by the above criteria, which constitutes its functional characteristics.

6. I understand that the claimed invention has been rejected by the United States Patent and Trademark Office as allegedly not being described in the application in such a way as to reasonably convey to one of ordinary skill in the relevant art that the

inventors, at the time the application was filed, had possession of the claimed invention.

7. Practicing the method of the invention requires monoclonal antibodies having inhibition characteristics as recited in the claims. As to the preparation of these monoclonal antibodies, it was standard practice as of January 17, 1996 for one skilled in this art to make a monoclonal antibody by immunizing a mouse with a particular immunogen, including a whole cell as an immunogen. Monoclonal antibody technology is a technology that was widely used and highly predictable as of January 17, 1996.

8. I was trained in the art of producing monoclonal antibodies as a Graduate student in 1979 and clearly understood the necessity for strict criteria for selection based on functional characterization by 1980. Although my first publication in the art was in 1983 (Kennedy et al., Characterization of anti-hepatitis B surface antigen monoclonal antibodies, Intervirology 19:176-180), this publication **(Exhibit 3)** clearly defines my understanding of the necessity for: (1) the proper structure of the immunogen, and; (2) defining the functional characteristics of the antibodies in question for their defined purpose. Since 1983 the art has changed and our understanding of the art has improved. In my assessment, based on the state of the art as of January 17, 1996, the innovative nature of the method claimed as the invention is: (1) the use of the particular immunogens

chosen (PM1 cells, HeLa cells, C8166 cells and protease digested human erythrocytes); (2) the selection of the monoclonal antibodies for their function of inhibiting fusion in accordance with the claimed method; and (3) the unexpected findings that fusion-inhibiting monoclonal antibodies did not recognize either CD4 or the HIV-1 envelope glycoprotein.

9. Based on the disclosure contained in the patent application, coupled with the general knowledge in the field about making monoclonal antibodies as of January 17, 1996, one skilled in the art could have readily made a monoclonal antibody having the fusion-inhibition characteristics recited in paragraph 5 above. Making monoclonal antibodies to cell surface markers on whole cells was a well-defined technology as of January 17, 1996. See Kohler and Milstein (1975) **(Exhibit 4)**. As of January 17, 1996, the level of skill of one of ordinary skill in the art of making a monoclonal antibody was a laboratory technician with a bachelor's degree and one to two years of experience working with hybridomas. Such a person of ordinary skill could have readily made a monoclonal antibody such as is recited in the claims for use in the method of the invention prior to January 17, 1996. In particular, the Experimental Details section of the applicants' specification teaches on pages 24-36 a straightforward, reproducible method for making and identifying appropriate monoclonal antibodies for use

in the method of the invention involving inhibiting HIV-1 infection of a CD4+ cell.

10. The application describes, among other things, the following information relevant to preparing antibodies which function in accordance with the method recited in the claims: a source of an immunogen for eliciting a monoclonal antibody for use in the claimed method (PM-1 cells, page 33, lines 9-11); a method for obtaining a monoclonal antibody by recovering supernatant from hybridomas generated by immunizing mice with PM1 cells (page 24); a screening assay called the resonance energy transfer ("RET") assay for identifying a monoclonal antibody having the fusion-inhibition characteristics required by the claimed method, i.e., the ability to inhibit HIV-1 envelope glycoprotein mediated membrane fusion (pages 25-26); adaptations to the RET screening assay such that HeLa cells expressing envelope glycoprotein from HIV-1_{JR-FL} ("HeLa-env_{JR-FL} cells") and HeLa cells expressing envelope glycoprotein from HIV-1_{LAI} ("HeLa-env_{LAI} cells") may be used for differential screening (page 25) for monoclonal antibodies having the fusion inhibition characteristics recited in the claims of the application; and monoclonal antibodies generated by immunizing mice with CD4+PM1 cells.

11. To prepare antibodies for use in practicing the claimed method, it is not necessary for one skilled in the art to know the antigenic determinants or epitopes on the whole cells used for immunization, or their

structural configuration. It is well established that having a starting immunogenic source such as an immunogenic whole cell and following an immunization method, a series of monoclonal antibodies will be elicited. It is also well established that the screening method allows one skilled in the art to identify and select monoclonal antibodies which, when contacted with a CD4+ cell in accordance with the claimed method, will (a) specifically inhibit 67% or greater of fusion of a CD4+ PM-1 cell to a HeLa cell expressing envelope glycoprotein from HIV-1_{JR-FL}, and (b) inhibits 18% or less of fusion of a CD4+ SUP-T1 cell to a HeLa cell expressing envelope protein from HIV-1_{LAI}, wherein the antibody (i) does not cross-react with HIV-1 envelope glycoprotein or CD4, (ii) reacts with an antigen on the surface of a PM-1 cell, and (iii) does not react with an antigen on the surface of a SUP-T1 cell, so as to thereby inhibit HIV-1 infection of the CD4+ cell.

12. Various immunogenic whole cells (such as PM1 cells, HeLa cells, C8166 cells and protease digested human erythrocytes) were used by applicants to generate monoclonal antibodies. One of the immunogenic whole cells (PM1 cells) resulted in eliciting antibodies that blocked fusion of CD4+PM1 cells to HeLa-env_{JR-FL} cells as identified by the screening methods. Thus the specification unequivocally shows that PM1 cells or analogous cells may be successfully used as an immunogen to make an HIV-1 fusion blocking antibody as disclosed in the specification which is

capable of operating in accordance with the method as recited in the claims. One of ordinary skill in the art could make, identify and select monoclonal antibodies in accordance with the present invention and thereby use such antibodies in a method of inhibiting HIV-1 infection of a CD4+ cell as recited in the claims of this application without any undue experimentation, as guided by the teachings of applicants' specification.

13. The application describes, in a manner clearly understandable to one of ordinary skill in this art, how to identify and select monoclonal antibodies meeting the requirements of the method of the claimed invention, i.e., as fitting the characteristics of inhibiting fusion between CD4+PM1 cells and HeLa-env_{JR-FL} cells by at least 67% and only inhibiting fusion between CD4+SUP-T1 cells and HeLa-env_{LAI} cells by at most 18%. In particular, pages 33-34 of the applicants' specification describe the inhibition of HIV-1 envelope glycoprotein-mediated membrane fusion in the RET assay by anti-PM1 hybridoma supernatants. Table 1 on page 34 summarizes the results achieved in experiments directed to the inhibition of HIV-1 envelope glycoprotein mediated cell fusion by the novel monoclonal antibodies disclosed for use with the claimed method of the invention. The data included in the Table clearly demonstrates that the PA-3, PA-5, PA-6 and PA-7 monoclonal antibodies specifically taught in the specification for use in the method of the invention, are capable, as recited in the claims,

of specifically inhibiting 67% or greater of fusion of a CD4+ PM-1 cell to a HeLa cell expressing envelope glycoprotein from HIV-1_{JR-FL}, and inhibiting 18% or less of fusion of a CD4+ SUP-T1 cell to a HeLa cell expressing envelope protein from HIV-1_{LAI}. Based upon the disclosure provided in the application one of ordinary skill in this art would be able to prepare a number of monoclonal antibodies, in addition to the specific examples denoted PA-3, PA-5, PA-6 and PA-7, having the fusion-inhibition characteristics recited in the claims, as described above.

14. The application also provides additional methods for further characterization of the fusion-inhibiting monoclonal antibodies useful in the method of the invention (see pages 26-30 and 34-36) demonstrating that the fusion-inhibiting monoclonal antibodies react with an antigen on the surface of a PM1 cell, do not react with HIV-1 envelope glycoprotein or CD4, and do not cross-react with an antigen on the surface of a SUP-T1 cell. Accordingly, the application provides detailed guidance and direction for making and choosing monoclonal antibodies having the characteristics as claimed, and for using such antibodies in a method of inhibiting HIV-1 infection of a CD4+ cell, wherein the method comprises contacting the CD4+ cell with an amount of the monoclonal antibody or portion thereof effective to (a) specifically inhibit 67% or greater of fusion of a CD4+ PM-1 cell to a HeLa cell expressing envelope glycoprotein from HIV-1_{JR-FL}, and (b) inhibit 18% or

less of fusion of a CD4+ SUP-T1 cell to a HeLa cell expressing envelope protein from HIV-1_{LAI}, wherein the antibody (i) does not cross-react with HIV-1 envelope glycoprotein or CD4, (ii) reacts with an antigen on the surface of a PM-1 cell, and (iii) does not react with an antigen on the surface of a SUP-T1 cell, so as to thereby inhibit HIV-1 infection of the CD4+ cell.

15. For one skilled in the art to practice the method of the invention as recited, for example, in claim 40, such individual need not know the structure of the antibody molecules which operate in accordance with the method. Rather, it is the function of these molecules, as defined by the above-described fusion-inhibition characteristics, which is the factor that controls the selection of the appropriate antibodies.

16. It is also clear that if the monoclonal antibodies meet the requirements and restrictions recited in claim 40, a monoclonal antibody which is a chimeric monoclonal antibody, a humanized monoclonal antibody, a human monoclonal antibody, and/or a monoclonal antibody that is a single-chain antibody or an antigen-binding fragment thereof will have identical requirements and restrictions as the originally defined monoclonal antibody. This was known by those of ordinary skill in this field prior to January 17, 1996.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that any such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 6/17/03

Ronald C. Kennedy

Ronald C. Kennedy, Ph.D.